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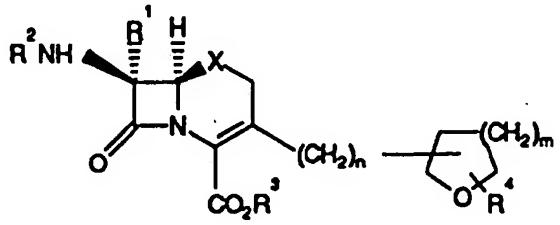
(54) Title: PROCESS FOR THE PREPARATION OF CEPHALOSPORINS AND ANALOGUES

(57) Abstract

A process for the preparation of cephalosporin compounds of formula (I) is disclosed, wherein R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group, in particular that of an antibacterially active cephalosporin; R^3 is a pharmaceutically acceptable *in vivo* hydrolysable ester group; R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alklyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S, SO, SO_2, O or CH_2; m is 1 or 2; and n is O. The process comprises the reaction of the corresponding carboxylic acid with a compound of formula R^3-Y, where Y is a halide radical, in the presence of an aqueous phase containing a base and a phase transfer catalyst. Subsequent removal of protecting groups, conversion of groups X and R^2 and salt formation may be carried out.



(I)

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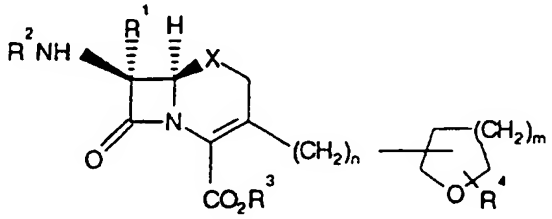
Process for the preparation of cephalosporins and analogues

This invention relates to novel processes for the preparation of cephalosporins. These cephalosporins have antibacterial properties, and are therefore of use in the treatment of bacterial infections in humans and animals caused by a wide range of organisms. The invention also relates to novel intermediates formed in the course of the process.

PCT application PCT/GB91/01228 (Beecham Group plc) discloses compounds of formula (I):



(I)

wherein

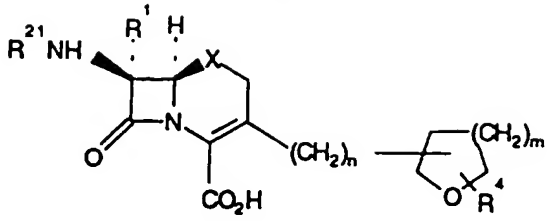
R^1 is hydrogen, methoxy or formamido;

R^2 is an acyl group, in particular that of an antibacterially active cephalosporin;

R^3 is a pharmaceutically acceptable <u>in vivo</u> hydrolysable ester group;

R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S,SO,SO_2,O or CH_2; m is 1 or 2; and n is 0. PCT/GB91/01228 also discloses process for the preparation of compounds of formula (I).

The present invention provides a process for the preparation of compounds of formula (I) as defined above, wherein an acid of formula (II):



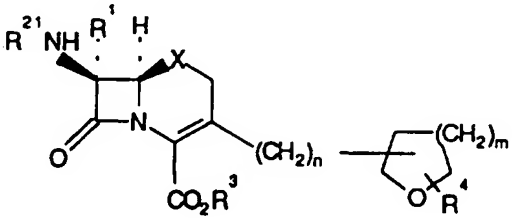
(II)

wherein R^1, R^4, X, m and n are as defined in formula (I) above, and R^{21} is a group R^2 as defined above or an amino-substituting or amino-protecting group different to R^2, is reacted with a compound of formula (III):

$$R^3 - Y$$

(III)

where Y is a halide radical, in an organic solvent which is at least partially immiscible with water, in the presence of an aqueous phase containing a base and a phase-transfer catalyst, to form a compound of formula (IV):



(IV)

where R^1, R^3, R^4, X, m and n are as defined above; and then if R^{21} is different to R^2, converting the compound of formula (IV) into a compound of formula (I) as defined above; and thereafter if necessary or desired, carrying out one or more of the following steps:

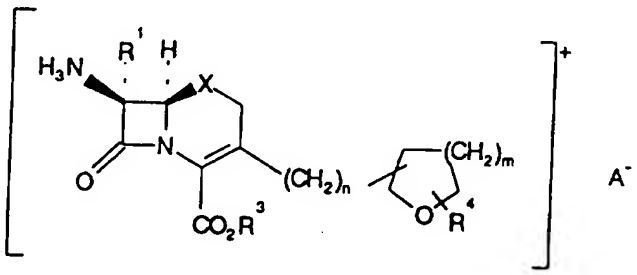
(i) removing any protecting groups,
(ii) converting the group X into a different group X,
(iii) converting the product into a salt,
(iv) converting group R^2 to a different group R^2.

The conversion of the compound of formula (IV) into a compound of formula (I) may for example be carried out by removal of the group R^{21} and its replacement by hydrogen so as to form a 7-amino analogue of the compound of formula (IV), followed by reaction of this 7-amino analogue with an acid of formula (V):

$$R^2\text{-OH} \qquad (V)$$

or an N-acylating derivative thereof where R^2 is an acyl group as defined in formula (I).

In a preferred embodiment the compound of formula (IV) may be converted into a compound of formula (VI):



(VI)

wherein R^1, R^3, R^4, X, m and n are as defined above, and A^- is a counter anion, followed by reaction of the compound of formula (VI) with an acid of formula (V) as defined above.

In compounds of formulae (I), (II), (IV) and (VI) the bonding carbon atom of the cyclic ether moiety which links the ring to the cephalosporin nucleus is generally asymmetric. The present invention includes either stereoisomer, as well as mixtures of both isomers.

In compounds of formula (I), (II), (IV) and (VI) where R^1 is formamido, the formamido group can exist in conformations wherein the hydrogen atoms of the -NH-CHO moiety are cis- or trans-; of these the cis conformation normally predominates.

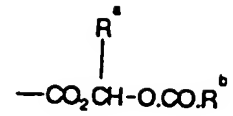
When used herein the term 'aryl' includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, hydroxy(C_{1-6})alkyl, mercapto(C_{1-6})alkyl, halo(C_{1-6}) alkyl, hydroxy, amino, nitro, carboxy, C_{1-6} alkylcarbonyloxy, alkoxycarbonyl, formyl, or C_{1-6} alkylcarbonyl groups.

The terms 'heterocyclyl' and 'heterocyclic' as used herein include aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. The term 'heteroaryl' refers to heteroaromatic heterocyclic rings suitably having 5 or 6 atoms in each ring. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

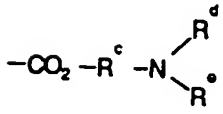
When used herein the terms 'alkyl' 'alkenyl', 'alkynyl' and 'alkoxy' include straight and branched chain groups containing from 1 to 6 carbon atoms, such as methyl, ethyl, propyl and butyl. A particular alkyl group is methyl.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine, and the term 'halide' is used correspondingly.

Examples of suitable pharmaceutically acceptable <u>in vivo</u> hydrolysable ester groups R^3 include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



(i)



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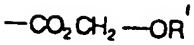

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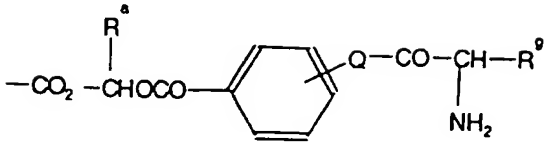
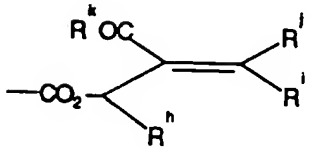


(iv)



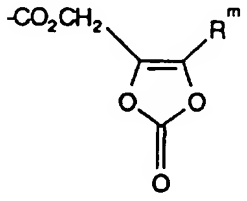
(v)

wherein R^a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, methyl, or phenyl, R^b is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, benzyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{1-6} alkyl C_{3-7} cycloalkyl, 1-amino C_{1-6} alkyl, or 1-(C_{1-6} alkyl)amino C_{1-6} alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents C_{1-6} alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent C_{1-6} alkyl; R^f represents C_{1-6} alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, C_{1-6} alkyl, or C_{1-6} alkoxy; Q is oxygen or NH; R^h is hydrogen or C_{1-6} alkyl; R^i is hydrogen, C_{1-6} alkyl optionally substituted by halogen, C_{2-6} alkenyl, C_{1-6} alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form C_{1-6} alkylene; R^j represents

hydrogen, C_{1-6} alkyl or C_{1-6} alkoxycarbonyl; and R^k represents C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable in vivo hydrolysable ester groups R^3 include, for example, acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; dialkylaminoalkyl especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-(alkoxycarbonyl)-2-alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl; and esters linked to a second β-lactam antibiotic or to a β-lactamase inhibitor.

A further suitable pharmaceutically acceptable in vivo hydrolysable ester group R^3 is that of the formula:



wherein R^5 is hydrogen, C_{1-6} alkyl or phenyl.

A preferred in vivo hydrolysable ester group is the pivaloyloxymethyl ester.

In compounds of formula (I), (II), (IV) and (VI), the group X may be sulphur or an oxidised sulphur atom, i.e. a sulphoxide (SO) or sulphone (SO_2) group. When X is a sulphoxide group it will be understood that α- and β-isomers may exist; both such isomers are encompassed within the scope of the present invention.

Examples of X include S, SO, SO_2 and CH_2.
Preferably X is sulphur or CH_2.

Advantageously, R^1 is hydrogen.

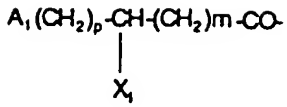
Suitably, the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted or substituted by up to three substituents, R^4, selected from C_{1-6} alkyl, for example methyl, C_{1-6} alkoxy, for example methoxy, C_{1-6} alkoxycarbonyl for example methoxycarbonyl, C_{1-6} alkoxy C_{1-6} alkyl, for example methoxymethyl, and C_{1-6} alkanoyloxy C_{1-6} alkyl, for example acetoxymethyl. Preferably the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted.

Preferably m is 1.

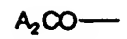
Preferably the cyclic ether is bonded to the cephalosporin nucleus at a ring carbon adjacent to the oxygen heteroatom.

Preferably the cyclic ether at the 3-position is a tetrahydrofuran-2-yl group, particularly an (S)-tetrahydrofuran-2-yl group.

Suitable acyl groups R^2 include those of formulae (a) - (f):



(a)



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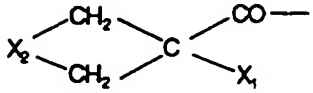
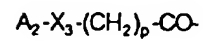
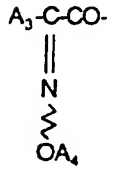


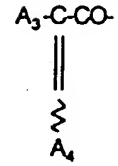
(c)



(d)



(e)



(f)

wherein p is 0, 1 or 2; m is 0, 1 or 2; A_1 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic (including heteroaromatic) group, such as phenyl, substituted phenyl, thienyl, pyridyl, or an optionally substituted thiazolyl group, a C_{1-6} akylthio group or C_{1-6} alkyloxy; X_1 is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group; A_2 is an aromatic group, for example a phenyl, 2,6-dimethoxyphenyl,2-alkoxy-1-naphthyl, 3-arylisoxazolyl, or a 3-aryl-5-methylisoxazolyl group, such as 3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl; a substituted alkyl group; or a substituted dithietane; X_2 is a $-CH_2OCH_2-$, $-CH_2SCH_2-$ or alkylene group; X_3 is an oxygen or sulphur atom; A_3 is an aryl or heteroaryl group such as phenyl, substituted phenyl, furyl,

aminothiazolyl or aminothiadiazolyl in which the amino group is optionally protected; and A_4 is hydrogen, C_{1-6}alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-6})alkyl, C_{1-6} alkoxycarbonyl(C_{1-6}) alkyl, C_{2-6} alkenyl, carboxy(C_{1-6})alkyl, C_{2-6} alkynyl, aryl or C_{1-6}alkyl substituted by up to three aryl groups.

Suitably when R^2 is a group (a), A_1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, cyclohexenyl, cyclohexadienyl, phenyl, substituted phenyl such as hydroxyphenyl, thienyl or pyridyl; and X_1 is a hydrogen or halogen atom, or a carboxy, carboxylic ester, azido, tetrazolyl, hydroxy, acyloxy, optionally protected amino, ureido, guanidino or acylureido group.

Suitably when R^2 is a group of formula (d), A_2 is phenyl, X_3 is oxygen and p is O.

Alternatively when R^2 is a group of formula (e) or (f) suitable values for the group A_3 include those commonly found in antibacterially active cephalosporins containing a hydroxyimino, substituted hydroxyimino or vinyl group in the side chain attached to position 7 of the cephalosporin nucleus, for example phenyl, thien-2-yl, thien-3-yl, fur-2-yl, fur-3-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-amino-1,2,4-thiadiazol-3-yl and 2-aminothiazol-4-yl in each of which the amino group is optionally protected.

Preferred groups for A_3 include phenyl, 2-aminothiazol-4-yl, fur-2-yl, thien-2-yl, 2-(2-chloroacetamido)thiazol-4-yl, 2-tritylamino-thiazol-4-yl, 5-amino-1,2,4-thiadiazol-3-yl and 4-aminopyrimid-2-yl.

In compounds of formula (I), a particularly preferred group for A_3 is 2-aminothiazol-4-yl.

Suitable values for the group A_4 include hydrogen, methyl, ethyl, cyclopropylmethyl, triphenylmethyl (trityl), cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, carboxymethyl, carboxypropyl and t-butoxycarbonylmethyl.

Preferred values for A_4 in compounds of formula (I) include methyl and hydrogen.

It will be appreciated that compounds of the invention wherein R^2 is a group of formula (e) (or (f)) can exist as syn and anti (or E and Z) isomers or mixtures thereof. Both isomers are encompassed within the scope of this invention.

Preferably the compounds of the invention wherein R^2 is a group of formula (e) have the syn configuration (i.e. have the group OA_4 syn to the amide linkage) or are enriched in that isomer.

Similarly, when R^2 is a group of formula (f), the group A_4 is preferably cis to the amide linkage, i.e. when group (f) is 2-amino-thiazol-4-yl, the Z-configuration is preferred.

It will be appreciated that also included within the scope of formula (I) are salts and carboxy-protected derivatives, including in vivo hydrolysable esters, of any carboxy groups that may be present as optional substituents in compounds of formula (I). Also included within the scope of the invention are acid addition salts of any amino group or substituted amino group that may be present as optional substituents in compounds of formula (I).

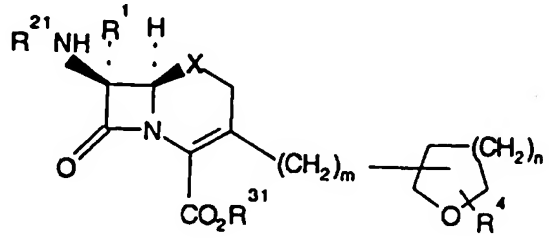
Certain compounds of formula (I), may, and compounds of formulae (II) and (IV) do include an amino group which is protected. Suitable amino protecting groups are those well known in the art which may be removed under conventional conditions without disruption of the remainder of the molecule.

Examples of amino protecting groups such as R^{21} include C_{1-6} alkanoyl, benzoyl, phenylacetyl, benzyl optionally substituted in the phenyl ring by one or two substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, halogen, or nitro; C_{1-4} alkoxycarbonyl; benzyloxycarbonyl or trityl substituted as for benzyl above; allyloxycarbonyl,trichloroethoxycarbonyl or chloroacetyl. An example of a group $R^{21}NH$ is phenylacetamido.

Formula (I) includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that

may be produced by processes such as lyophilisation.

Acids of formula (II) above may be prepared from known (see PCT/GB 91/01228) compounds of formula (VII):



(VII)

where R^1, R^{21}, R^4, X, m and n are as defined above, and R^{31} is a carboxylate-protecting group, by removal of the group R^{31} to leave a carboxylic acid group.

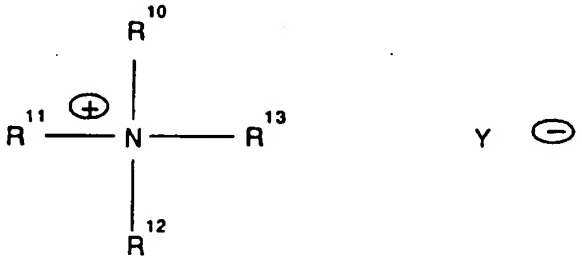
Suitable readily removable carboxylate protecting groups R^{31} include groups forming ester derivatives of the carboxylic acid, including in vivo hydrolysable esters. The derivative may be one which may readily be cleaved in vivo.

Suitable ester-forming carboxylate-protecting groups are those which may be removed under conventional conditions. Such groups R^{31} include benzyl, 4-methoxybenzyl, benzoylmethyl, 4-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, 4-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus- containing group, an oxime radical of formula -N=CHR where R is aryl or heterocyclic, or an in vivo hydrolysable ester radical such as defined below.

A carboxylic acid group may be regenerated from any of the above esters by usual methods appropriate to the particular R^{31} group, for example, acid- and base- catalysed hydrolysis, or by enzymically-catalysed hydrolysis, or by hydrogenolysis under conditions wherein the remainder of the molecule is substantially unaffected.

For example when R^{31} is a 4-methoxybenzyl group the carboxylic acid group may be regenerated by reaction of the compound of formula (VII) with aluminium chloride in the presence of anisole, in an organic solvent such as dichloromethane, for example at -50°C to 0°C. The acid (II) so formed may then be purified by formation of the sodium salt in aqueous solution, acidification and extraction of the acid (II) so formed into an organic solvent such as dichloromethane.

For the reaction between the acid of formula (II) and the compound of formula (III) a suitable organic solvent is dichloromethane. The base may for example be an inorganic base, such as a Group I or II metal hydroxide, carbonate or bicarbonate, or a Group II metal oxide, such as sodium or potassium hydroxide, carbonate or bicarbonate, calcium or magnesium oxide, carbonate or hydroxide etc. Organic bases such as organic amines, for example triethylamine or pyridine may also be used. The phase transfer catalyst and the base may be the same compound, or a separate base and catalyst may be used. Suitable phase-transfer catalysts include quarternary ammonium salts, for example those of formula (VIII):



(VIII)

wherein Y^- is an anion, R^{10} and R^{11} are C_{1-18} organic groups, R^{12} is a C_{1-10} alkyl group, R^{13} is a C_{1-6} alkyl group, R^{11}, R^{12} and R^{13} and the nitrogen to which they are attached can form a pyridine system.

Suitable examples of the groups R^{10} and R^{11} are C_{1-18} straight chain alkyl groups, and, more generally, C_{1-18} hydrocarbon groups which may contain one or more hetero atoms and which are joined to nitrogen through saturated carbon atoms.

The anion Y^- may be an inorganic anion, provided it is in practice inert under the reaction conditions, for example a halide such as chloride,

bromide or iodide. Conveniently the anion Y^- may be a hydroxide ion, so that the compound (VIII) may function both as a base and as the phase transfer catalyst, and so that a separate base in the aqueous phase may not be necessary.

Suitably the phase-transfer catalyst may be a tetrabutylammonium salt, for example a halide, used in combination with a separate base. Preferably the catalyst is tetrabutylammonium hydroxide, functioning both as the catalyst and as a base.

The compound (III) may be any halide of the group R^3, for example a chloride, bromide or iodide. Conveniently the compound (III) may be pivaloyloxymethyl iodide, to introduce a pivaloyloxymethyl group R^3 into the compound (IV). If Y is an iodide radical it is desirable to include a reducing agent such as a metabisulphite into the aqueous phase as a stabiliser.

Conversion of the compound (IV) into the ammonium salt (VI) may be carried out by removal of the amino-substituting or amino-protecting group R^{21} to leave an NH_2 group, followed by formation of the salt. Removal of R^{21} may be achieved by the Delft procedure commonly used in β-lactam chemistry. Suitable reaction conditions include treatment with phosphorus pentachloride and and N-methylmorpholine at reduced temperatures, e.g. -20°C to + 10°C. The 7-amino compound so produced may then be reacted with the acid HA to form the salt (VI). The anion A^- in (VI) may be any in practice inert inorganic or organic anion which is known to form salts with 7-amino cephem compounds, for example halide (e.g. chloride, bromide, iodide), hydrogen sulphate, alkyl sulphonate such as methane sulphonate, hydrogen tartrate, aryl sulphonate, such as benzene sulphonate, or toluene-4-sulphonate. Suitably the acid HA and the 7-amino compound may be reacted together in an organic solvent such as ethyl acetate.

Acids of formula (V) are known (see for example PCT/GB 91/01228), or may be prepared by methods known in the art, or methods analogous to such processes. Suitable processes include those described for example in GB 2107307, GB 1536281, and GB 1508064.

A reactive N-acylating derivative of the acid (V) may be employed in the process. The choice of reactive derivative will of course be influenced by the chemical nature of the substituents of the acid.

Suitable N-acylating derivatives include an acid halide, preferably the acid chloride or bromide or alternatively a symmetrical or mixed anhydride. The acylation may be effected in the presence of an acid binding agent for example, tertiary amine (such as pyridine or dimethylaniline), molecular sieves, an inorganic base (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds hydrogen halide liberated in the acylation reaction. The oxirane is preferably a (C_{1-6})-1,2-alkylene oxide - such as ethylene oxide or propylene oxide. The acylation reaction using an acid halide may be carried out at a temperature in the range -50°C to +50°C, preferably -20°C to +20°c, in aqueous or non-aqueous media such as water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, dichloromethane, 1,2-dichloroethane, or mixtures thereof. Alternatively, the reaction may be carried out in an unstable emulsion of water-immiscible solvent, especially an aliphatic ester or ketone, such as methyl isobutyl ketone or butyl acetate. The acylation with acid halide or anhydride is suitably carried out in the presence of a basic catalyst such as pyridine or 2,6-lutidine.

Acid halides may be prepared by reacting the acid (V) or a salt or a reactive derivative thereof with a halogenating (eg chlorinating or brominating) agent such as methane sulphonyl chloride, phosphorus pentachloride, thionyl chloride, oxalyl chloride or phosgene.

Suitable mixed anhydrides are anhydrides with, for example, carbonic acid monoesters, trimethyl acetic acid, thioacetic acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric, phosphorous, and phosphinic acids) or aromatic or aliphatic sulphonic acids (such as p-toluenesulphonic acid or methanesulphonic acid).

Alternative N-acylating derivatives of acid (V) are the acid azide, or activated esters such as esters with 2-mercaptopyridine, cyanomethanol, p-nitrophenol, 2,4-dinitrophenol, thiophenol, halophenols, including pentachlorophenol, monomethoxyphenol, N-hydroxy succinimide,

N-hydroxybenzotriazole, or 8-hydroxyquinoline; or amides such as N-acylsaccharins, N-acylthiazolidin-2-thione or N-acylphthalimides; or an alkylidene iminoester prepared by reaction of the acid (V) with an oxime.

Other reactive N-acylating derivatives of the acid (V) include the reactive intermediates formed by reaction in situ with a condensing agent such as a carbodiimide, for example, N,N'-diethyl-, dipropyl- or diisopropylcarbodiimide, N,N'-di-cyclohexyl-carbodiimide, or N-ethyl-N'-[3-(dimethylamino)propyl]- carbodiimide; a suitable carbonyl compound, for example, N,N'-carbonyldiimidazole or N,N'-carbonyldi-triazole; an isoxazolinium salt, for example, N-ethyl-5-phenylisoxazolinium-3-sulphonate or N-t-butyl-5-methylisoxazolinium perchlorate; or an N-alkoxycarbonyl 2-alkoxy-1,2-dihydroquinoline, such as N-ethoxycarbonyl 2-ethoxy-1,2-dihydroquinoline. Other condensing agents include Lewis acids (for example BBr_3 - C_6H_6); or a phosphoric acid condensing agent such as diethylphosphorylcyanide. The condensation reaction is preferably carried out in an organic reaction medium, for example, methylene chloride, dimethylformamide, acetonitrile, alcohol, benzene, dioxan or tetrahydrofuran.

A further method of forming the N-acylating derivative of the acid of formula (V) is to treat the acid of formula (V) with a solution or suspension preformed by addition of a carbonyl halide, preferably oxalyl chloride, or a phosphoryl halide such as phosphorus oxychloride, to a halogenated hydrocarbon solvent, preferably dichloromethane, containing a lower acyl tertiary amide, preferably N,N-dimethylformamide. The N-acylating derivative of the acid of formula (V) so derived may then be caused to react with a compound of formula (II). The acylation reaction may conveniently be carried out at -40° to +30°C, if desired in the presence of an acid binding agent such as pyridine. A catalyst such as 4-dimethylaminopyridine may optionally also be added. A preferred solvent for the above acylation reaction is dichloromethane.

The optional reduction step, the optional conversion of R^2 to a different R^2 and X to a different X, and the optional formation of a salt, may be carried out using methods well known in the art of cephalosporin and penicillin chemistry.

For example, when the group X is S, SO, or SO_2, the group X may be converted into a different group X by methods of oxidation or reduction well known in the art of cephalosporin and penicillin synthesis, as described, for example, in EP-A-0 114 752. For example, sulphoxides (in which X is SO) may be prepared from the corresponding sulphide (in which X is S) by oxidation with a suitable oxidising agent, for example an organic peracid such as m-chloroperbenzoic acid.

A reduction step is generally effected by processes well known in the art of β-lactam chemistry, for example using phosphorus trichloride in dimethylformamide.

In the process described hereinabove, and in the process described hereinbelow, it may be necessary to remove protecting groups. Deprotection may be carried out by any convenient method known in the art such that unwanted side reactions are minimised. Separation of unwanted by-products may be carried out using standard methods.

It is particularly preferred to use the above-described process for the preparation of the following compounds:

Pivaloyoxymethyl(6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methyoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate,

Pivaloyloxymethyl (6*R*,7*S*)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyimino-acetamido]-3-[(*S*)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate

Compounds of formula (VI) are believed to be novel and are a further aspect of the present invention.

The invention will now be described by way of example only.

EXAMPLE 1

Pivaloyloxymethyl (6*R*,7*R*)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyimino-acetamido]-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate

a) Pivaloyloxymethyl (6*R*,7*R*)-7-phenylacetamido-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate

Aluminium trichloride (1.526g, 11.4mmol) was added to anisole (10ml) in dichloromethane (20ml) at <-20°C and stirred 0.25h. The mixture was cooled to -40°C and 4-methoxybenzyl (6*R*,7*R*)-7-phenylacetamido-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate (1.893g, 3.7mmol) in dichloromethane (30ml) added. Stirred 0.25h at -40°C then sodium bicarbonate (4.188g, 50mmol) in 0.1M pH7 sodium phosphate buffer (75ml) added and stirred vigorously for 0.25h. The mixture was filtered through a celite pad, the layers separated, the dichloromethane extracted with dilute aqueous sodium bicarbonate then the aqueous solutions were combined, washed twice with ether, dichloromethane (20ml) added and the vigorously stirred mixture adjusted to pH2.4 with 5N sulphuric acid. The organic phase was collected, the aqueous extracted twice with dichloromethane (10ml) then water (20ml) added to the combined organic solution and the stirred mixture adjusted to pH6.5 with 10% tetrabutylammonium hydroxide. Sodium metabisulphite (0.2g) then pivaloyloxymethyl iodide [prepared from pivaloyloxymethyl chloride (2.10g) and sodium iodide (1.90g) in acetone (5ml)] added. The reaction was stirred and maintained at pH6.5 with 10% tetrabutylammonium hydroxide for 0.5h then toluene (25ml) and ethyl acetate (75ml) added, the dichloromethane removed *in vacuo* and the organic phase collected, washed three times with water then with brine, dried, concentrated and flash chromatographed on silica gel eluting with 35% ethyl acetate in hexane to give the *title compound* as a colourless foam (1.660g, 89%); ν_{max} (CH_2Cl_2) 3412, 1787, 1751, 1687, 1507, 1124, 1097, 1054 and 995cm^{-1}; δ_H ($CDCl_3$) 1.22 (9H, s), 1.4-1.65 (1H, m), 1.85-2.05 (2H, m), 2.25-2.45 (1H, m), 3.27 and 3.59 (2H, ABq, *J* 18.25Hz), 3.62 and 3.68 (2H, ABq, *J* 16.25Hz), 3.75-4.0 (2H, m), 4.86 (1H, dd, *J* 9.07, 6.70Hz), 4.94 (1H, d, *J* 4.64Hz), 5.81 and 5.89 (2H, ABq, *J* 5.48Hz), 5.85 (1H, dd, *J* 9.15, 4.65Hz), 5.98 (1H, d, *J* 9.12Hz) and 7.2-7.45 (5H, m); *m/z* (CI, +ve ion, ammonia)

503 (MH^+), 520 (MNH_4^+).

b) Pivaloyloxymethyl (6*R*,7*R*)-7-amino-3-[(*S*)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate

Phosphorus pentachloride (1.887g, 9.2mmol) in dichloromethane (47ml) was added to pivaloyloxymethyl (6*R*,7*R*)-7-phenylacetamido-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate (3.082g, 6.14mmol) and *N*-methylmorpholine (1.4ml, 12.3mmol) in dichloromethane (50ml) at <-20°C. Stirred 0.5h at -7.5+5°C then methanol (15ml) added quickly, stirred 0.75h then water (50ml) added and stirred vigorously for 1h. The dichloromethane was removed *in vacuo*, ethyl acetate (25ml) added and the mixture stirred and adjusted to pH7.0 with .880 ammonia. The organic layer was collected, aqueous extracted with ethyl acetate (25ml) and the combined ethyl acetate solutions dried, concentrated and flash chromatographed on silica gel eluting with 40-50% ethyl acetate in hexane to give the *title compound* as a foam (1.950g, 83%); (Found: 384.1359; $C_{17}H_{24}N_2O_6S$ requires 384.1355); ν_{max} (CH_2Cl_2) 1779, 1751, 1623, 1481, 1349, 1122 and 1054cm^{-1}; δ_H ($CDCl_3$) 1.23 (9H, s), 1.5-1.8 (3H, m obscured by bs), 1.9-2.1 (2H, m), 2.3-2.5 (1H, m), 3.34 and 3.49 (2H, ABq, *J* 18.71Hz), 3.8-4.05 (2H, m), 4.77 (1H, d, *J* 4.99Hz), 4.87 (1H, dd, *J* 9.06, 6.68Hz), 4.93 (1H, d, *J* 5.12Hz) and 5.84 and 5.88 (2H, ABq, *J* 5.50Hz); *m/z* (CI, +ve ion, ammonia) 385 (MH^+), 402 (MNH_4^+).

c) Pivaloyloxymethyl (6*R*,7*R*)-7-amino-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate toluene-4-sulphonic acid salt

Phosphorus pentachloride (1.469g, 7.14mmol) in dichloromethane (37ml) was added to pivaloyloxymethyl (6*R*,7*R*)-7-phenylacetamido-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate (2.387g, 4.75mmol) and *N*-methylmorpholine (1.05ml, 9.55mmol) in dichloromethane (40ml) at <-20°C. Stirred 0.5h at -7.5+5°C then methanol (10ml) added quickly, stirred 0.75h then water (20ml) added and stirred vigorously for 1h. The dichloromethane was removed *in vacuo*, ethyl acetate (25ml) added and the mixture stirred and adjusted to pH7.0 with .880 ammonia. The organic layer was collected, aqueous extracted with ethyl acetate (15ml) and the combined ethyl acetate solutions dried. Toluene-4-sulphonic acid hydrate (0.907g, 4.77mmol) in ethyl acetate (10ml) was added, the

solution concentrated *in vacuo* to ~20ml and set aside. After 1h the crystals were collected, washed with cold ethyl acetate and dried *in vacuo* to give the *title compound* as colourless needles (1.638g, 62%); m.p. 177 - 180°C; (Found: C, 51.81; H, 5.90; N, 5.17; S, 11.62. $C_{24}H_{32}N_2O_9S_2$ requires C, 51.79; H, 5.79; N, 5.03; S, 11.52%); ν_{max} (CH_2Cl_2) 1792, 1751, 1269, 1213, 1158, 1125 and 1009cm^{-1}; δ_H ($CDCl_3$) 1.20 (9H, s), 1.3 - 1.5 (1H, m), 1.8 - 2.0 (2H, m), 2.2 - 2.4 (1H, m), 2.35 (3H, s), 3.28 (2H, s), 3.84 (2H, t, *J* 6.71Hz), 4.84 (1H, d, *J* 4.67Hz), 4.95 (1H, d, *J* 4.62Hz), 5.08 (1H, dd, *J* 8.63, 7.08Hz), 5.81 and 5.83 (2H, ABq, *J* 5.60Hz), 7.13 and 7.76 (4H, ABq, *J* 8.06Hz) and 8.79 (3H, bs).

d) Pivaloyloxymethyl (6*R*,7*R*)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate

Methanesulphonyl chloride (154µl, 2mmol) was added to 2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetic acid (402mg, 2mmol) and diisopropylethylamine (350µl, 2mmol) in DMF (5ml) at <-40°C. The reaction was stirred at -40+5°C for 0.5h then pivaloyloxymethyl (6*R*,7*R*)-7-amino-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate (0.688g, 1.79mmol) in DMF (4ml) followed by pyridine (162µl) were added. The mixture was stirred 0.5h without further cooling then diluted with ethyl acetate, washed successively with water, 5% citric acid solution, water, saturated sodium bicarbonate, water and saturated brine then dried, evaporated *in vacuo* and flash chromatographed on silica gel eluting with 75% ethyl acetate in hexane to give the *title compound* as a foam (0.901g, 89%); ν_{max} ($CHCl_3$) 3490, 3405, 3350, 1776, 1749, 1681, 1532 and 1055cm^{-1}; δ_H ($CDCl_3$) 1.23 (9H, s), 1.55-1.75 (1H, m), 1.9-2.05 (2H, m), 2.3-2.5 (1H, m), 3.37 and 3.66 (2H, ABq, *J* 18.82Hz), 3.8-4.0 (2H, m), 4.07 (3H, s), 4.92 (1H, dd, *J* 8.94, 6.89Hz), 5.08 (1H, d, *J* 4.79Hz), 5.45 (2H, bs), 5.84 and 5.91 (2H, ABq, *J* 5.46Hz), 6.06 (1H, dd, *J* 9.00, 4.83Hz), 6.79 (1H, s) and 7.76 (1H, d, *J* 8.88); *m/z* (FAB, +ve ion, thioglycerol) 568 (*MH*$^+$).

EXAMPLE 2

Pivaloyloxymethyl (6*R*,7*S*)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyimino-acetamido]-3-[(*S*)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate

a) Pivaloyloxymethyl (6*R*,7S)-7-phenylacetamido-3-[(*S*)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate

Aluminium trichloride (552mg, 4.15mmol) was added to anisole (4ml) in dichloromethane (8ml) at <-20°C and stirred 0.25h. The mixture was cooled to -40°C and 4-methoxybenzyl (6*R*,7*S*)-7-phenylacetamido-3-[(S)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate (700mg, 1.43mmol) in dichloromethane (10ml) added. Stirred 0.25h at -40°C then sodium bicarbonate (1.41g, 16.8mmol) in water (20ml) added and stirred vigorously for 0.25h.The pH was adjusted to 2.2 with 5N sulphuric acid and the organic phase was collected. The aqueous phase was extracted twice with dichloromethane (10ml) and then the combined organic layers washed with water. Water (20ml) added to the organic solution and the pH adjusted to 6.5 with 10% tetrabutylammonium hydroxide. Sodium metabisulphite (74mg) then pivaloyloxymethyl iodide [prepared from pivaloyloxymethyl chloride (744mg) and sodium iodide (595mg) in acetone (3ml)] added. The reaction was stirred overnight and maintained at pH6.5 with 10% tetrabutylammonium hydroxide. The organic layer was separated, washed twice with water then with brine, dried, concentrated and chromatographed on silica gel eluting with 70% ethyl acetate in hexane to give the *title compound* as a pale yellow foam (551mg, 80%); (Found: M^+ 484.2215; $C_{26}H_{32}N_2O_7$ requires M 484.2210); ν_{max} (CH_2Cl_2) 3417, 1769, 1736, 1681, 1506 and 1387cm^{-1}; δ_H ($CDCl_3$) 1.12 (1H,m), 1.21 (9H, s), 1.51 (1H, m), 1.89-2.00 (3H, m), 2.26-2.43 (3H, m), 3.58 and 3.66 (2H, ABq, J 15.9Hz), 3.78-3.95 (3H, m), 4.89 (1H, dd, J 9.0, 6.8Hz), 5.28 (1H, dd, J 6.2,5.0Hz), 5.79 and 5.91 (2H, ABq, J 5.7Hz), 5.88 (1H, obscured) and 7.20-7.35 (5H, m); m/z (CI, +ve ion, ammonia) 485 (MH^+), 502 (MNH_4^+).

b) Pivaloyloxymethyl (6*R*,7*S*)-7-amino-3-[(*S*)-tetrahydrofuran-2-yl]-1- carba-1-dethiaceph-3-em-4-carboxylate

Phosphorus pentachloride (420mg, 2.02mmol) in dichloromethane (10ml) was added to pivaloyloxymethyl (6*R*,7*S*)-7-phenylacetamido-3-[(*S*)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate (660mg, 1.36mmol) and *N*-methylmorpholine (0.30ml, 2.73mmol) in

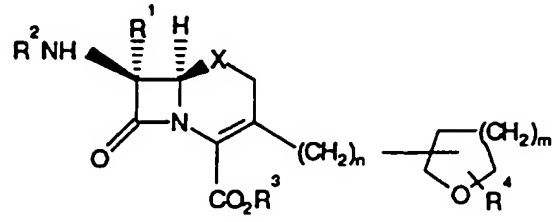
dichloromethane (12ml) at <-20°C. Stirred 0.75h at -10±5°C then methanol (3ml) added quickly, stirred 0.75h then water (6ml) added and stirred vigorously for 1h. The dichloromethane was removed *in vacuo*, ethyl acetate (15ml) added and the mixture stirred and adjusted to pH7.0 with .880 ammonia. The organic layer was collected, aqueous extracted with ethyl acetate (25ml) and the combined ethyl acetate solutions dried, concentrated and chromatographed on silica gel eluting with 5% methanol in ethyl acetate to give the *title compound* as a foam (289mg, 58%); (Found: M^+ 366.1796; $C_{18}H_{26}N_2O_6$ requires M 366.1791); ν_{max} (CH_2Cl_2) 1759, 1734 and 1123cm^{-1}; δ_H ($CDCl_3$) 1.23 (9H, s), 1.31-1.52 (2H, m), 1.61 (2H, br.s.,exch.), 1.90-2.16 (3H, m), 2.28-2.48 (3H, m), 3.70-3.97 (3H, m), 4.51 (1H, d, J 5.4Hz), 4.90 (1H, dd, J 9.0, 6.8Hz) and 5.82 and 5.92 (2H, ABq, J 5.5Hz); m/z (CI, +ve ion, ammonia) 367 (MH^+), 384 (MNH_4^+).

c) **Pivaloyloxymethyl (6*R*,7*S*)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-3-[(*S*)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate**

Methanesulphonyl chloride (65µl, 0.84mmol) was added to 2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetic acid (169mg, 0.84mmol) and diisopropylethylamine (147µl, 0.84mmol) in DMF (7ml) at <-40°C. The reaction was stirred at -40±5°C for 0.5h then pivaloyloxymethyl (6*R*,7*S*)-7-amino-3-[(*S*)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate (280mg, 0.77mmol) in DMF (5ml) followed by pyridine (68µl, 0.84mmol) were added. The mixture was stirred 1h at 0°C then diluted with ethyl acetate, washed successively with saturated sodium bicarbonate, 5% citric acid solution, water (X2), and saturated brine then dried, evaporated *in vacuo* and chromatographed on silica gel eluting with ethyl acetate to give the *title compound* as a foam (280mg, 67%); (Found:M^+549.1911.$C_{24}H_{31}N_5O_8S$ requires 549.1893); ν_{max} (CH_2Cl_2) 3486, 1758, 1674, 1532 and 1387cm^{-1}; δ_H ($CDCl_3$) 1.23 (9H, s), 1.50-1.72 (2H, m), 1.92-2.52 (6H, m), 3.71-3.90 (3H, m), 4.00 (3H, s), 4.93 (1H, dd, J 8.8, 6.9Hz), 5.64 (1H, dd, J 7.7, 5.0Hz), 5.66 and 5.82 (2H, ABq, J 5.6Hz), 6.02 (2H, br.s., exch.) 6.77 (1H, s) and 8.29 (1H, d, J 7.7Hz); m/z (CI, +ve ion, ammonia) 550 (MH^+).

Claims

1. A process for the preparation of compounds of formula (I):



(I)

wherein

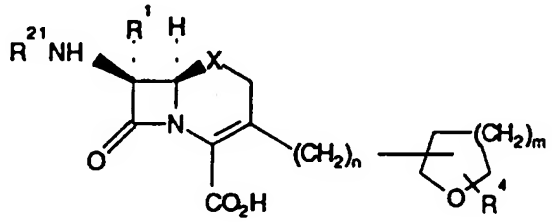
R^1 is hydrogen, methoxy or formamido;

R^2 is an acyl group, in particular that of an antibacterially active cephalosporin;

R^3 is a pharmaceutically acceptable in vivo hydrolysable ester group;

R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S,SO,SO_2,O or CH_2; m is 1 or 2; and n is 0:

wherein an acid of formula (II):



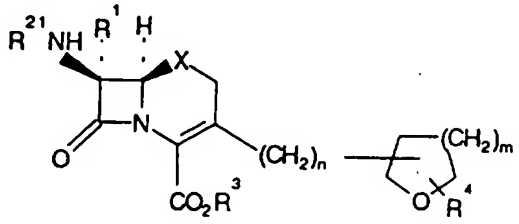
(II)

wherein R^1, R^4, X, m and n are as defined in formula (I) above, and R^{21} is a group R^2 as defined above or an amino-substituting or amino-protecting group different to R^2, is reacted with a compound of formula (III):

R^3 - Y

(III)

where Y is a halide radical, in an organic solvent which is at least partially immiscible with water, in the presence of an aqueous phase containing a base and a phase-transfer catalyst, to form a compound of formula (IV):



(IV)

where R^1, R^3, R^4, X, m and n are as defined above; and then if R^{21} is different to R^2, converting the compound of formula (IV) into a compound of formula (I) as defined above; and thereafter if necessary or desired, carrying out one or more of the following steps:

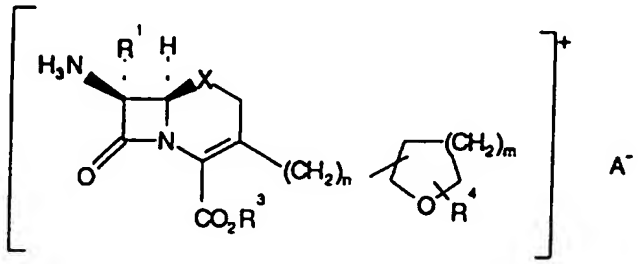
(i) removing any protecting groups,
(ii) converting the group X into a different group X,
(iii) converting the product into a salt,
(iv) converting group R^2 to a different group R^2.

2. A process according to claim 1 wherein the conversion of the compound of formula (IV) into a compound of formula (I) is carried out by removal of the group R^{21} and its replacement by hydrogen so as to form a 7-amino analogue of the compound of formula (IV), followed by reaction of this 7-amino analogue with an acid of formula (V):

R^2-OH (V)

or an N-acylating derivative thereof where R^2 is an acyl group as defined in formula (I).

3. A process according to claim 1 wherein the compound of formula (IV) is converted into a compound of formula (VI):



(VI)

wherein R^1, R^3, R^4, X, m and n are as defined above, and A^- is a counter anion, followed by reaction of the compound of formula (VI) with an acid of formula (V) as defined in claim 2.

4. A process according to any one of claims 1 to 3 wherein R^3 is pivaloyloxymethyl.

5. A process according to any one of claims 1 to 4 wherein the base and the phase-transfer catalyst are tetrabutylammonium hydroxide.

6. A process according to any one of the preceding claims wherein Y is iodide.

7. A process according to claims 3 wherein A^- is toluene-4-sulphonate.

8. A process according to any one of the preceding claims wherein the compound of formula I is selected from:

Pivaloyloxymethyl (6*R*,7*R*)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*)-methoxyimino-acetamido]-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate, and

Pivaloyloxymethyl (6*R*,7*R*)-7-[2-(2-aminothiazol-4-yl)-2-[(*Z*)-methoxyimino-acetamido]-3-[(S)-tetrahydrofuran-2-yl]-1-carba-1-dethiaceph-3-em-4-carboxylate.

9. A compound of formula (VI) as defined in claim 3.

10. A compound accoridng to claim 9 being pivaloyloxymethyl (6*R*,7*R*)-7-amido-3-[(*S*)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate toluene-4-sulphonic acid salt.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/GB 95/02783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/20 C07D463/00 C07D501/18 C07D505/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 01695 (BEECHAM GROUP PLC) 6 February 1992 see claims	1-10
A	WO,A,94 00457 (SMITH-KLINE BEECHAM PLC) 6 January 1994 see claims	1-10
A	WO,A,93 11131 (SMITH-KLINE BEECHAM PLC) 10 June 1993 see claims	1-10
A	WO,A,92 04353 (BEECHAM GROUP PLC) 19 March 1992 see claims	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
4 March 1996	8.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Luyten, H

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INTERNATIONAL SEARCH REPORT

Interr. al Application No
PCT/GB 95/02783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

Intern: al Application No
PCT/GB 95/02783

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